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TABLE OF CONTENTS

	PAGE
FRONT COVER	1
SF 298 REPORT DOCUMENTATION	2
TABLE OF CONTENTS	3
INTRODUCTION	4
BODY	4
KEY RESEARCH ACCOMPLISHMENTS	8
REPORTABLE OUTCOMES	9
CONCLUSIONS	9
REFERENCES	10
APPENDICES	

DOES SUBSEQUENT PREGNANCY INFLUENCE BREAST CANCER SURVIVAL?

Ruby T. Senie, Catherine Schaefer, Jeanne Petrek

INTRODUCTION:

The quality of life of some young breast cancer patients may be influenced by clinical recommendations regarding subsequent childbearing. Limited data has been published on the impact of pregnancy following diagnosis, an option that is more readily considered today than in the past. However, new treatment protocols including radiation after breast conserving surgery as well as chemotherapy may impact reproductive decision making while influencing disease free survival. Since the duration of chemotherapy protocols has recently been reduced, some women to retain or regain their menstrual cycles and pregnancy after breast cancer may be possible (1). However, as Beatson reported a century ago, some oncologists still propose bilateral oophorectomy to reduce the risk of metastases (2), while others encourage their patients to delay childbearing decisions due to fear of stimulating recurrent disease resulting from high hormonal levels of pregnancy. However, patient advocates have requested studies to address several quality of life issues including the safety of pregnancy after primary and adjuvant breast cancer treatment (3). Published data from several countries with nationalized health care programs have reported no adverse effect of childbearing after breast cancer(4,5); however, few of these investigations were able to adequately control for cancer status in cases being compared and several prospective analyses could not rule out selection bias (6). This collaborative retrospective study, being conducted to assess the impact on breast cancer survival of subsequent pregnancy, has been made facilitated by collaborators of the Kaiser Permanente Research Foundation. As in other studies conducted by Kaiser investigators, the extensive medical records maintained of all members of this Kaiser HMO located in northern California enabled the identification of breast cancer cases diagnosed during the past thirty years for this nested case-case study (7).

BODY:

Overview of Scope of Work

Linkage of datafiles in addition to extensive abstracting of patient medical records maintained by the Kaiser Permanente Medical Care Program (KPMCP) in Northern California has enabled the identification of breast cancer cases diagnosed before the age of 45 with and without a history of pregnancy after initial detection of disease. The goal has been assessment of survival differences in relation to post-treatment pregnancy history.

A unique life-long medical record number assigned to each member at the time of initial enrollment in the Kaiser program enables record linkage between data sets. Computerized cancer and hospitalization datafiles enabled the identification of 114 women age less than 45 at diagnosis who had one or more pregnancies after diagnosis of breast cancer. The identification of four comparison cases without a post-diagnosis pregnancy matched as closely as possible on age and year of diagnosis, stage of disease and

months of survival before the first subsequent pregnancy is nearly complete. The nested case-case comparison study has been conducted within the population of breast cancer cases identified through linkage of several data sets. All data collection has been performed by researchers and staff of the Kaiser Permanente Research Foundation.

- The Kaiser Permanente Regional Cancer Registry enabled the identification of breast cancer cases treated since 1970; cases diagnosed during more recent years have also been recorded in SEER files for the Bay Area hospitals and the California State Cancer Registry.
- The Membership Database provides administrative records with information on age, sex, address, and years of membership in the KPMCP. This file indicates that the membership of some study patients was not continuous in the KP Health Plan either prior to or after breast cancer diagnosis. Since gaps in their enrollment history have been noted, some reproductive events or recurrences may have occurred during these intervals. During medical record review all reproductive events and treatment factors are abstracted potentially providing information about events occurring during intervals without Kaiser membership. For some study subjects data collection during such intervals will not be possible.
- The Kaiser Permanente Regional Hospitalization Registry files provide the dates of hospital admissions providing information about any pregnancies after the date of breast cancer diagnosis.
- The California Automated Mortality Linkage and Information System enables identification of deaths occurring in the breast cancer cases included in this study who remained residents of California. National death records are also assessed to determine deaths among study subjects who may have moved from California.
- Kaiser Medical Records have been abstracted to provide epidemiologic information, prognostic factors, treatment information, and disease status at follow-up. Medical records supplement computerized follow-up information. Essential data from medical records includes stage of breast cancer at diagnosis, cancer treatment, and disease status during follow-up. KPMCP members are not restricted to specific outpatient facilities; therefore, records related to their medical history before and after breast cancer treatment are maintained at more than one site requiring the abstractors to visit several KPMCP facilities to retrieve all necessary data. During chart review, abstractors identified some breast cancer cases who were pregnant at the time of data collection. To assess the influence on prognosis, these cases will need to be assessed again before the study results are finalized. Date of death has also captured from the patient's medical record but charted date of death is not considered as accurate or complete as state data from the California mortality files and from the National Death Index.

The work scope of the project has included:

- Link the case records with birth records to identify women who have had one or more pregnancies after breast cancer diagnosis. Dates of diagnosis and pregnancy outcome are compared in order to eliminate women who were pregnant at the time of diagnosis of breast cancer.[Figure 1]
- Match each case with a positive history of subsequent pregnancy to four breast cancer patients without a history of subsequent pregnancy. To meet the maximum number of matching criteria in order to identify 4 controls for each case, some flexibility in age and year of diagnosis was required. Other essential aspects of the matching criteria such as stage of disease at time of subsequent pregnancy of the case necessitated reviewing more medical records than initially anticipated. [Figure 1]

Matching criteria for 4 comparison cases without subsequent pregnancy for each case with a positive history include:

- a) age at diagnosis
 - b) year of diagnosis
 - c) stage at diagnosis
 - d) months of survival from diagnosis to first subsequent pregnancy
 - e) disease status during the first trimester of the first subsequent pregnancy
- Abstract data from medical records retained in multiple outpatient and inpatient KPMCP facilities using a standardized data collection instrument to obtain demographic and health history information including:
 - a) prior pregnancy history
 - b) family history of breast cancer at time of diagnosis
 - c) tumor size and nodal status at diagnosis
 - d) primary and adjuvant treatment administered.

A member of the Kaiser research staff trained in medical record abstracting has handled data collection directed by Dr. Catherine Schaefer.

- Perform matched statistical analyses to compare the risk of recurrence and death due to breast cancer of women with a positive history of subsequent pregnancy with matched cases. Initial data analyses identified specific questions that resulted in the need for further abstracting and follow-up data. For this reason this study was not able to be completed in three years as originally planned; therefore, a no-cost extension was requested and granted.

Computerized Data

The figures 1 and 2 describe the linking of the baseline data abstracting for the total study population to SEER follow-up data, California Vital Statistics Death Records, and the National Death Index to produce the composite dataset for transfer to the research team of Columbia for statistical analyses. No personal identifying data will be included. However, the unique KPMCP medical record number will be

scrambled before inclusion in the data file. Members of the Division of Research of KPMCP have retained a file with both the scrambled and actual medical record number in order to identify subjects if questions pertaining to individual cases arise during analysis.

Current status of research project

Computerized files identified 114 cases with one or more post diagnosis pregnancies. Each medical record was obtained to carefully review the cancer history and to abstract the essential data for the planned matched survival analyses. Data abstraction for these cases has been completed. Linkage of the abstracted data with current data files to obtain date of last contact, years of membership in Kaiser, years of survival and/or current cancer status have been performed. All data have been computerized by Kaiser staff.

Women, negative for subsequent pregnancy, were identified by computer-linked data files and careful chart review. To date 351 comparison cases have been identified. Figure 1 in the Appendix describes the methodology used to identify the 114 breast cancer cases with a history of post diagnosis pregnancy and the currently identified 351 matched cases with a negative subsequent pregnancy history. Some cases have been found during medical record abstracting to have a history of spontaneous miscarriage or induced abortion that did not require hospitalization. These cases have been added to the subset with a positive history of subsequent pregnancy. For all cases found through record review to have a positive post-treatment pregnancy, four control cases will be selected from the cohort with a negative history.

During medical record abstracting the date of breast cancer diagnosis on the pathology report is used to verify the computerized record; dates of diagnosis and pregnancy outcome are compared to eliminate women who were pregnant at the time of diagnosis of breast cancer. Only pregnancies initiated after diagnosis are included. Of the 114 cases identified, 56% carried one or more subsequent pregnancies to term; interrupted pregnancies including abortion [32%] and miscarriage [10%] were also documented. One woman experienced an ectopic pregnancy. Only one subsequent pregnancy was documented for 72% of the cases; 28% had two or more post diagnosis pregnancies.

Preliminary data from the available computer file indicate that the study cases were diagnosed between 1970 and 1995. No more than 5 calendar years separated the date of diagnosis of 96% of the cases with a positive pregnancy history and their matched comparison cases. Age at diagnosis ranged from 18 to 45 with a mean of 33 without significant differences by subsequent pregnancy history indicating that matching was successful. Stage of disease was nearly identical for the two subsets; 20% were noted as having in situ disease, 54% local stage without axillary metastases and 26% regional stage with positive axillary nodes. Approximately 20% of each group were nulliparous at the time of diagnosis of breast cancer.

Preliminary analyses have been conducted to compare survival among cases with and without a history of subsequent pregnancy indicating that 31% of each group had experienced recurrent disease and 23%

had died of breast cancer. These survival assessments were based on incomplete data and may differ from the results in the final report.

When the final data set has been received from our Kaiser colleagues, matched analyses will be performed as planned in the initial study design. Potential prognostic factors, not included as matching variables, such as prior pregnancy history and family history of breast cancer, will be controlled for in the Cox proportional hazards models. Additional analyses limited to cases with a positive history will address prognostic differences by age at diagnosis and age at subsequent pregnancy. If the number of cases with a positive history of subsequent pregnancy permits, the length of the interval between diagnosis and first subsequent pregnancy, pregnancy outcome, and number of post treatment pregnancies will be studied in relation to survival.

Activities to be conducted in Year 4

Due to the added time required for our colleagues of the Kaiser Division of Research to provide a complete dataset, the following will be conducted during the 12 months of our no-cost extension:

- Kaiser staff will finalize the composite datafiles for transfer to Columbia
- Survival analyses of matched sets with and without subsequent pregnancy will be conducted by Columbia staff in collaboration with Dr Ann Zauber of Memorial Sloan Kettering
- Study findings will be reviewed with co-investigators
- Final report and manuscript will be prepared

The analytic procedures used in this study are divided into two sections. The first aspect of the analysis will compare risk of recurrence and death due to breast cancer among cases with and without a subsequent pregnancy history. The second phase will focus on women with a positive history, assessing any survival differences related to months between diagnosis and first post-treatment pregnancy, total number of pregnancies, and pregnancy outcomes.

KEY RESEARCH ACCOMPLISHMENTS

- 114 cases with one or more post diagnosis pregnancies identified
- Data abstraction from medical records of these 114 cases has been completed
- 351 matched cases without a history of subsequent pregnancy have been identified
- Data abstraction from medical records of these 351 matched cases has been completed
- Files have been linked with Kaiser membership records and SEER records
- Initial data analyses have been conducted revealing the need for additional data abstraction
- Data files have been linked to obtain follow-up information on current survival and/or cancer status

REPORTABLE OUTCOMES

The abstract, including preliminary results, reported at the Department of Defense Era of Hope meeting in June is included in the appendix. However, these results may be modified when the final dataset is analyzed.

CONCLUSIONS

This research project benefits from the long history of Kaiser Permanente and the computerized data to identify breast cancer cases treated since 1970. The large number of breast cancer cases treated by Kaiser clinicians during the past 30 years, extensive treatment, pregnancy information and follow-up data enable this project to assess the impact on survival of subsequent pregnancy while taking into consideration the effect of breast cancer stage at diagnosis and adjuvant treatment.

Information stored in computerized files provided the basis for matching cases; however, some essential data elements were only obtained by careful abstraction of medical records; therefore, this project has required greater time and effort than initially proposed. For this reason the project has not yet been completed. An additional factor that has required special handling pertains to locating women who were diagnosed and initially treated by Kaiser clinicians but who discontinued their membership in the Kaiser HMO. Some former subscribers have moved from the geographic region covered by the HMO while others may have received health care through other insurance programs. Obtaining information on the current status of these women may require additional effort although Kaiser has an active follow-up program as required by the SEER program of northern California.

This interim report will be followed by a final report by September 2001 when a manuscript will be submitted for consideration of publication.

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DOES SUBSEQUENT PREGNANCY INFLUENCE BREAST CANCER SURVIVAL?

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Among young breast cancer patients, desires for future childbearing may impact treatment decisions. Recently, the duration of chemotherapy has been reduced increasing the likelihood of some young women retaining their fertility and their ability to achieve pregnancy. However, many oncologists encourage their patients to delay childbearing fearing recurrent disease may be stimulated by hormonal elevations of pregnancy. Studies assessing the impact of subsequent pregnancy have been limited by small sample size and/or inability to control for disease status in comparison cases at time of subsequent pregnancy.

The current retrospective chart review study is being conducted collaboratively with researchers of the Kaiser Permanente Research Foundation in Northern California, an established HMO with extensive medical records maintained on all patients. Computerized cancer and hospitalization datafiles enabled the identification of 114 women age <45 at diagnosis who had one or more subsequent pregnancies. Four comparison cases without a post-diagnosis pregnancy are being selected from the same datafiles. Comparison cases are matched as closely as possible on age and year of diagnosis, stage of disease and months of survival before the first subsequent pregnancy. Data on disease recurrence and death is abstracted from medical records, California mortality files, and the National Death Index.

To date 344 comparison cases have been identified. All cases were diagnosed in a Kaiser affiliated hospital between 1970 to 1995. Reported SEER tumor stage indicated 20% were *in situ*, 54% with local disease, and 26% with regional disease. Only 20% of those with a subsequent pregnancy were nulliparous at diagnosis; 56% of the subsequent pregnancies were carried to term, 10% were terminated by miscarriage and 32% by induced abortion. Preliminary analyses are being performed to assess the matching criteria of each set.

Survival analyses for matched sets will be conducted to assess the risk of recurrence and death due to breast cancer among 114 cases with subsequent pregnancy compared 456 cases without post-diagnosis pregnancies. Prognostic factors known to influence breast cancer survival will be included in the Cox proportional hazards models.

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APPENDICES

Figure 1: File Linkage for Case Identification

Figure 2: File Linkage for Survival Analyses

**Abstract : Era of Hope Breast Cancer Research Meeting
June 8-11, 2000 Atlanta, GA**

Figure 1

Does subsequent pregnancy influence breast cancer survival?

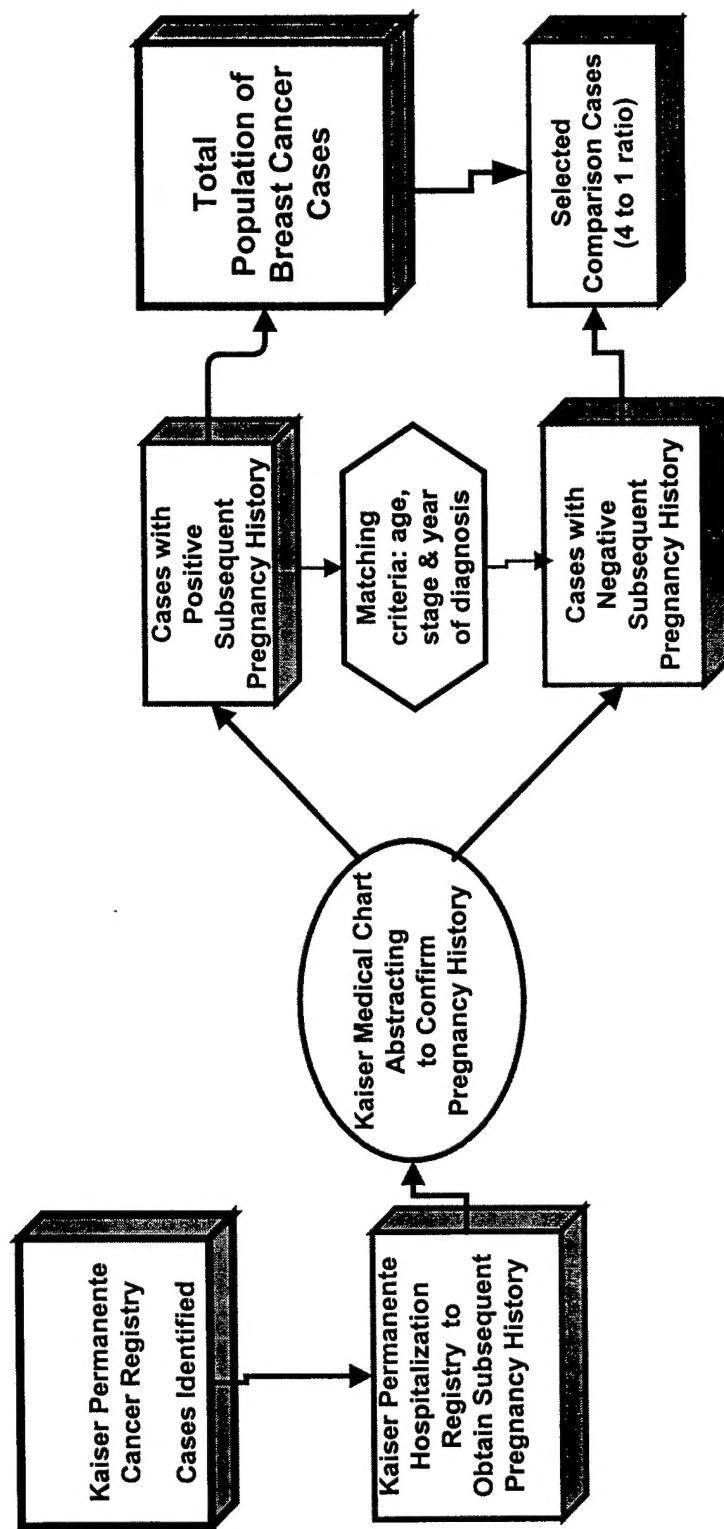


Figure 2

Does subsequent pregnancy influence breast cancer survival?

